

On page 4, please replace the paragraph spanning lines 15-18 with the following new paragraph:

--These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

A2 **FIGURE 1a, 1b and 1c** shows the promoter region of human 5-HT1A from -3438 to -393 (SEQ ID NO:1). The position of the polymorphism at -1017 is shown by an arrow.--

Please replace the paragraph spanning page 5, line 18 through page 6, line 2, with the following paragraph:

A3 --**FIGURE 5** shows the detection of the C-G polymorphism at -1017 bp of the 5-HT1A gene in human blood samples. Fig. 5A is the wild type sequence with a C at position -1017. Fig. 5B shows a heterozygous individual for the mutation, with both a C and G at position -1017 bp. Fig. 5C is the homozygous mutant sequence, showing a G at position -1017. The repressive region of the human 5-HT1A promoter was analyzed for length and size variations using blood samples from depressed patients and normals. A 718-bp fragment was amplified by PCR and sequenced within the region of the promoter between -1593 to -876 bp of the initial ATG codon. Shown is DNA sequence analysis in the region of -1017 bp from PCR products of 3 different patients which revealed patients with: the wild-type sequence A (figure shows positions 2411-2433 of SEQ ID NO:1), with a C at position -1017 from the initial ATG codon; sequence heterozygous for the mutation with both a C and a G nucleotide at -1017 bp, corresponding to sequence B (figure shows positions 2411-2433 of SEQ ID NO:1 with the indicated mutation shown at position 2422); and sequence homozygous for a C-G mutation (sequence C) (figure shows positions 2411-2433 of SEQ ID NO:1 with the mutation shown at position 2422) --

On page 6, please replace the paragraph spanning lines 17-25 with the following paragraph:

A4 --The present invention relates to a DNA sequence of the 5' flanking region of the 5-HT1A receptor gene, from about -3438 to about -393 (SEQ ID NO:1), wherein said sequence contains a mutation that results in an inhibition of protein-DNA interactions. The novel DNA sequence can be used as a genetic marker in a diagnostic or prognostic test for mental illnesses that involve the

Q4 serotonin system. This invention further relates to proteins, which bind to this region and the use of said proteins to develop therapeutics to treat depression and related illnesses that involve the serotonin system. this invention also relates to a glucocorticoid-responsive element located from about -393 to the ATG initiation codon of the 5-HT1A receptor gene.--

Please replace the paragraph spanning page 14, line 18 through page 15, line 5, with the following paragraph:

Q5 --Blood samples from depressed patients were collected following extensive characterization of the patients for clinical drug trial. Documentation of the patients tested is included in Appendix 1. DNA samples from a random pool of normal individuals were also collected. The blood samples were either amplified directly or subjected to DNA extraction before amplification using optimal PCR conditions and primers. DNA extraction from whole blood samples was done using the Split Second DNA Preparation Kit (Boehringer Mannheim). When used directly, diluted blood samples were, prior to PCR amplification, subjected to three heat and cool cycles at 95°C and 55°C. PCR primers were designed to amplify a -718 bp fragment of the human 5-HT1A 5'-flanking region from -1593 to -876 bp of the initial ATG codon. The sense primer had the following sequence: 5'-GTGGCGAACATAAAACCTCA-3' (SEQ ID NO:3), and the antisense primer had the following sequence: 5'-TTCTTAAATCGTGTGTCAGCATC-3' (SEQ ID NO:4). PCR products were electrophoresed on a 1.0% agarose gel and DNA bands were purified, free of oligonucleotide primers, using the QIAEX II Gel Extraction Kit (Qiagen). Purified DNA was then heat-denatured at 95°C and snap-cooled in an ethanol/dry ice bath followed by a 30-min. annealing with PCR primers. Preparation was then sequenced using the Sanger dideoxy termination method (T7 sequencing kit, Pharmacia biotech).--

On page 19, please replace the paragraph spanning lines 3-22 with the following paragraph:

Q6 --The identification of a polymorphic change that correlates with major depression raises the important question of whether the -1017 bp region has functional activity. This region participates in the cell-specific basal repression of the 5-HT1A receptor gene based on its general location. Functional activity is demonstrated by the presence of a complex in nuclear protein extracts that

binds specifically to a 31-bp region flanking -1017 bp (Fig. 6). As detected by gel mobility shift assay, in the presence of nuclear extract from raphe RN46A cells several complexes were detected compared to without extract (lane 1). However, only the complex indicated was susceptible to competition with unlabeled specific 31-bp oligonucleotide, but not by an unrelated oligonucleotide, indicating a specific interaction. The other complexes may represent high capacity/low affinity interactions with the poly-A repeat segment of the 31-bp oligonucleotide. Thus, RN46A cells contain a specific nuclear complex that interacts with the -1017-bp region of the 5-HT1A receptor.

At Within the sequence flanking the C-G site (double-underlined) is a palindrome indicated in bold 5'-**AACGAAGACNNNNNNNGTCTTCTT**-3' (SEQ ID NO:2). The palindrome forms a structure that is recognized by DNA binding proteins. For example, steroid receptors recognize palindromic sequences as specific DNA binding sites (Evans, 1988). The C-G mutation may alter the stability of protein-DNA interactions at this site resulting in a change in 5-HT1A receptor expression or regulation.--
